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SnapShot: Spinal Cord Development

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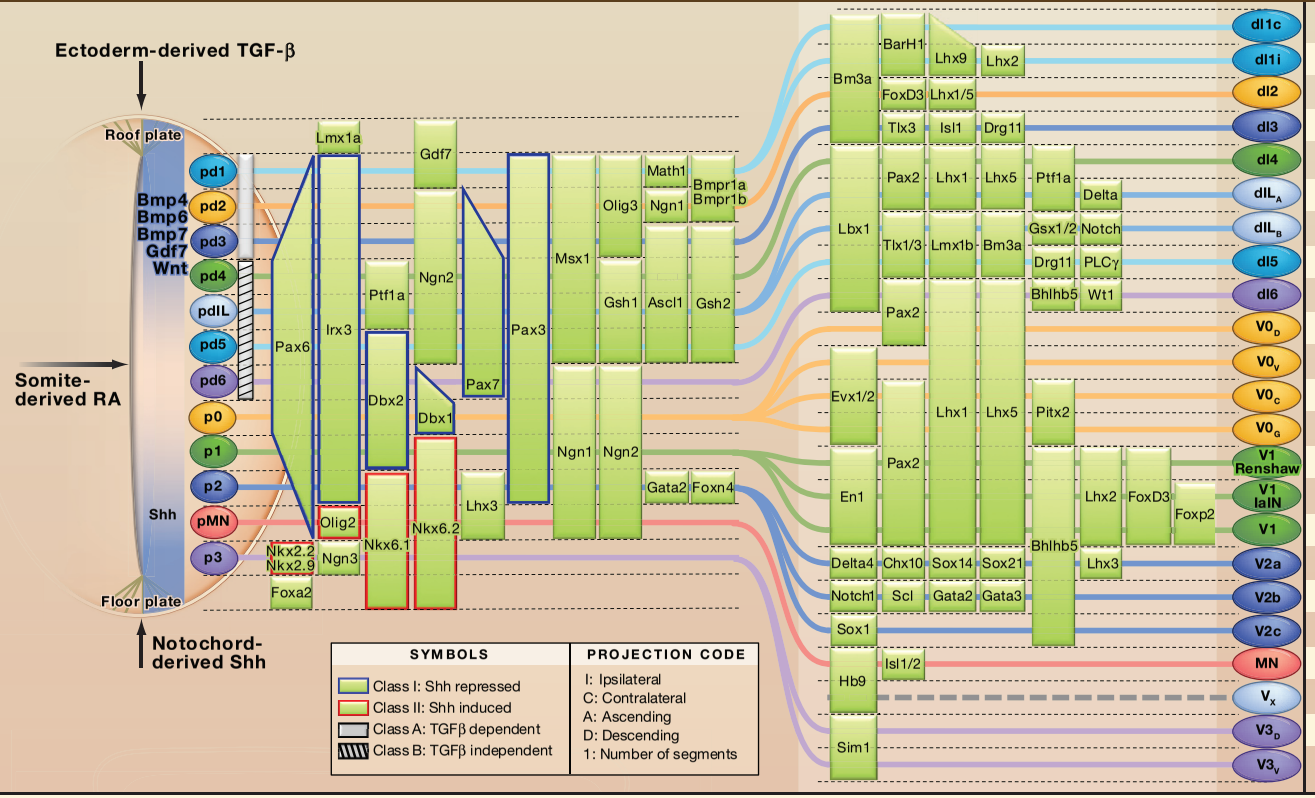
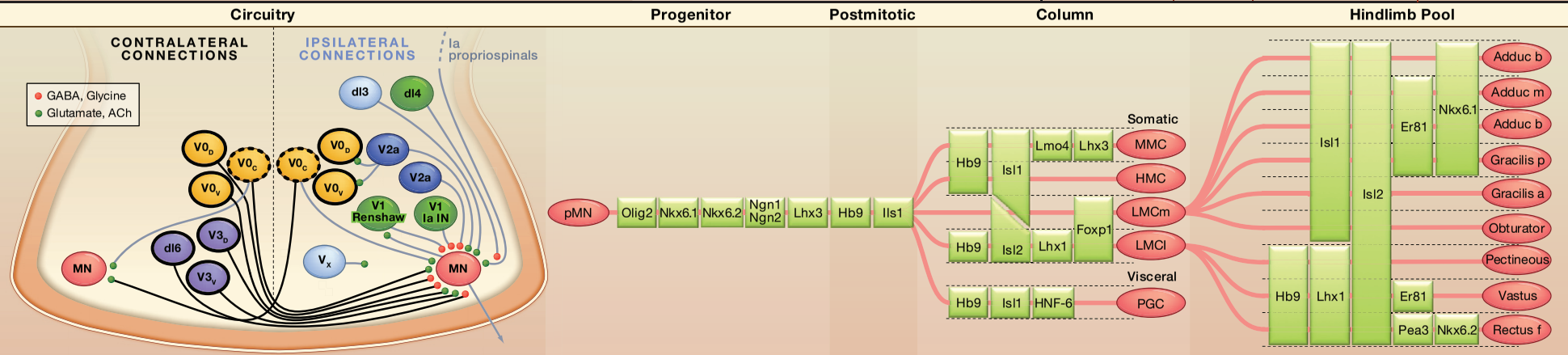
Cell



Cell Type	Neurotransmitter	Projection	Target	Role
dI1c	Glutamate	CA>2	Cerebellum	Somatosensory relay
dI1i	Glutamate	IA>2	Cerebellum	Somatosensory relay
dI2	Glutamate	CA<D	Thalamus	Somatosensory relay
dI3	Glutamate	IA<D	Motor neurons	Somatosensory relay
dI4	GABA	I<2	Cutaneous afferents proprioceptive terminals	Somatosensory associative
dIL$_A$	GABA	C<2	Dorsal horn interneurons	Somatosensory associative
dIL$_B$	Glutamate	C AD	Dorsal horn interneurons	Somatosensory associative
dI5	Glutamate	C<2	Dorsal horn interneurons	Somatosensory associative
dI6	GABA/Glycine	C AD	Ventral interneurons MNs	L/R coordination?
V0$_D$	GABA Glycine	C	MN	L/R coordination
V0$_V$	GABA Glycine	C D 1-3	MN, IaIN	Motor function
V0$_C$	Acetylcholine	IC D 1-3	MN, Renshaw	Motor output amplitude
V0$_G$	Glutamate	?	MN, V0	Motor function
V1 Renshaw	Glycine GABA	I D 1-3	MN, IaIN	Recurrent inhibition of MNs
V1 IaIN	Glycine GABA	I D 1-3	MN, Renshaw	Reciprocal inhibition
V1	Glycine GABA	?	?	Rate
V2a	Glutamate	I A>D>2	MN, V0	L/R coordination
V2b	GABA Glycine	I A>D>2	INs	F/E?
V2c	GABA Glycine?	?	?	?
MN	Acetylcholine	Muscle	Muscle	Contraction of musculature
V$_X$	Glutamate	?	?	Motor function
V3$_D$	Glutamate	C A>D>2	MN, V1, V2	Rhythmicity
V3$_V$	Glutamate	C A>D>2	MN, V1, V2	Rhythmicity



See online version for legend and references.

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Cell

This SnapShot outlines the sequential genetic steps that generate neuronal diversity within an idealized spinal segment of the mouse. The progression from neural progenitor cells to postmitotic neurons spanning embryonic day 9.5 (e9.5) to e18.5 is shown from left to right, although some events are not strictly linear. Diverse combinations of Hox transcription factor expression along the rostrocaudal (i.e., head-to-tail) axis further subdivide motor neurons, but for clarity, these patterns are not reflected in this idealized segment. Recent studies have begun to define the functions of the cardinal cell types in the spinal cord, particularly those that relate to locomotor behaviors.

Precursor Generation

Cellular identities are defined by the influence of a two-dimensional coordinate system of morphogen gradients that act on the neuroepithelial cells occupying the ventricular zone of the ~e9.5 neural tube. A Sonic hedgehog (Shh) gradient produced by the notochord and the floor plate establishes the identity of five ventral progenitor cell domains (p0, p1, p2, pMN, and p3), marked by the expression transcription factors with a basic-helix-loop-helix (bHLH) domain and a homeodomain. Genes repressed by Shh are categorized as class I (e.g., *Irx3*), and genes induced by Shh are termed class II (e.g., *Olig2*). Typically, the transcription factors in adjacent progenitor domains repress expression of factors in neighboring domains, preventing cells from developing with hybrid identities. Transforming growth factor β (TGFβ) family proteins from the overlying ectoderm (e.g., *Bmp4*) and roof plate (e.g., *Gdnf7*) produces dorsalizing signals. The dorsal-most progenitor domains, pd1–pd3, depend on TGFβ, whereas pd4–pd6 and pdlL are independent of TGFβ. The somite produces retinoic acid (RA) that controls subtype and dorsoventral identity through *Pax6*. Within this idealized segment of spinal cord, these morphogen gradients establish 12 progenitor domains that grossly give rise to seven dorsal interneuron progenitor divisions, pd1–6 and pdlL; four ventral interneuron progenitor divisions, p0–3; and one motor neuron progenitor domain, pMN. Ventral progenitor domains (e.g., pMN) produce one cell type early (e.g., motor neurons) followed by another cell type later (e.g., oligodendrocytes).

Refinement and Subdivision of Classes

As cells mature within their respective progenitor zones and begin to exit the cell cycle, an abrupt transition occurs in the transcriptional profile of cells. The postmitotic cells from some progenitor domains (e.g., p2) become further diversified through intercellular signaling interactions (e.g., Notch-Delta), which leads to the generation of excitatory V2a and inhibitory V2b neurons from common ancestral progenitor cells. As neuron development progresses, the neurotransmitter properties of the cells emerge, and they express phenotypic markers, such as neurotransmitter biosynthetic enzymes (e.g., choline acetyltransferase [*ChAT*] or glutamic acid decarboxylase [*GAD*]) and vesicular transport proteins (e.g., *vGluT2*). Many progenitor domains tend to give rise to neurons with similar initial axonal growth trajectories; however, the pd1, p1, and p0 domains produce interneuron subtypes with diverse axonal projections, which are clear exceptions to this trend. The diversification of a single neuronal class is best exemplified by motor neurons.

Motor Neurons

Motor neurons are subdivided by their cell body positions within motor columns. Each motor column consists of multiple motor pools that innervate individual muscles. Generic postmitotic motor neurons become subdivided into the medial and hypaxial motor columns (MMC and HMC), which innervate the back (epaxial) and trunk (hypaxial) musculature, respectively. At limb levels, the medial and lateral portions of the lateral motor column (LMCm and LMCl) innervate the ventral and dorsal portions of the limb, respectively. Additional motor neurons form the autonomic nervous system as preganglionic (PGC) cholinergic neurons of sympathetic and parasympathetic targets. Pools of motor neurons innervating the same muscle can be defined by unique combinations of transcription factors (e.g., *Nkx6* and *Ets* classes).

Locomotor Circuitry

The spinal interneurons and motor neurons comprise a central pattern-generating circuitry that is capable of producing rhythmic left-right and flexor-extensor alternation in isolated cords, called fictive locomotion. Molecular genetic studies have defined roles for several classes of interneurons found in the ventral cord. Mutant mice lacking contralaterally projecting inhibitory *Dbx1*$^+$ V0 class interneurons display a disorganized left-right alternation. Use of diphtheria toxin to ablate ipsilaterally projecting excitatory *Chx10*$^+$ V2a cells also disturbs right-left alternation and, notably, at higher speeds, animals transition to a left-right synchronous gallop that is not seen in wild-type mice. Loss or inactivation of ipsilateral inhibitory *En1*$^+$ V1 neurons results in a marked slowing of locomotion, whereas inactivation of contralaterally projecting excitatory *Sim1*$^+$ V3 interneuron class disrupts the regularity of the rhythm. Inactivation of the *Pitx2*$^+$ $V0_C$ class disrupts locomotion during swimming due to altered integration of sensory feedback. The ipsilaterally projecting glutamatergic *Hb9*$^+$ V_x class is rhythmically active during locomotion. The *Ptf1a*$^+$ dI4 class forms inhibitory presynaptic contacts on glutamatergic proprioceptive sensory neurons in the ventral spinal cord. The dI6 and dI3 interneuron classes make direct connections onto motor neurons; however, their roles have not been determined.

Abbreviations

Ascl1, achaete-scute complex homolog 1 (*Drosophila*); BarH1, BarH-like homeobox; Bhlhb5, basic-helix-loop-helix family, member e22; Bmp2, bone morphogenetic protein 2; Bmp4, bone morphogenetic protein 4; Bmp5, bone morphogenetic protein 5; Bmp6, bone morphogenetic protein 6; Bmp7, bone morphogenetic protein 7; Bmpr1a, bone morphogenetic protein receptor, type 1a; Bmpr1b, bone morphogenetic protein receptor, type 1b; Brn3a, POU domain, class 4, transcription factor 1; Chx10, visual system homeobox; Dbx1, developing brain homeobox; Dbx2, developing brain homeobox; Isl1, ISL1 transcription factor, LIM homeodomain; Isl2, ISL2 transcription factor, LIM homeodomain; Lbx1, ladybird homeobox homolog 1; Lhx1, LIM homeobox protein 1; Lhx2, LIM homeobox protein 2; Lhx4, LIM homeobox protein 4; Lhx5, LIM homeobox protein 5; Lhx9, LIM homeobox protein 9; Lmo4, LIM domain only 4; Lmx1b, LIM homeobox transcription factor 1 beta; Math1, atonal homolog 1 (*Drosophila*); Msx1, homeobox, msh-like 1; Ngn1, neurogenin 1; Ngn2, neurogenin 2; Ngn3, neurogenin 3; Notch, Notch gene homolog 1 (*Drosophila*); Nkx2.2, NK2 transcription factor related locus 2; Nkx2.9, NK2 transcription factor related, locus 9; Nkx6.1, NK6 homeobox 1; Nkx6.2, NK6 homeobox 2; Olig2, oligodendrocyte transcription factor 2; Olig3, oligodendrocyte transcription factor 3; Pax2, paired box gene 2; Pax3, paired box gene 3; Pax6, paired box gene 6; Pax7, paired box gene 7; PLCgamma, phospholipase C, gamma 1; Ptf1a, pancreas-specific transcription factor 1a; Pitx2, paired-like homeodomain transcription factor 2; RA, retinoic acid; Scl, T cell acute lymphocytic leukemia 1; Shh, Sonic hedgehog; Sim1, single-minded homolog 1; Sox1, SRY box-containing gene 1; Sox14, SRY box-containing gene 14; Sox21, SRY box-containing 21; Tlx1/3, T cell leukemia, homeobox 1/3; Wt1, Wilms tumor homolog 1.

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